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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/540,402	06/30/2006	Yoram Groner	2488.017	8368

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EXAMINER	
SGAGIAS, MAGDALENE K	
ART UNIT	**PAPER NUMBER**
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/540,402	GRONER ET AL.	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above claim(s) *14-48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/26/06;9/28/05;6/23/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-48 are pending.

Applicant's election with traverse of Group I in the reply filed on 2/5/07 is acknowledged. The traversal is on the ground(s) that the requirement for unity of invention is fulfilled for a group of inventions that are so linked as to form a single general inventive concept. Applicants argue the claims of Group VIII are directly related to claims of Groups I and II, which are drawn to a method for the treatment using an agent, which up regulates RUNX3 expression. Applicants argue the claims of Group I and II are related in that they are both directed to a method for up regulating RUNX3 expression in cells. Applicants argue that Groups V and VII are related in that they are drawn to a diagnostic kit for use in conjunction with the claimed methods. This is not found persuasive because applicant has not pointed to any errors in the examiner's reasoning for the restriction/election requirement. The central issue is this application is national stage application of an international filing. The MPEP is clear that national stage applications follow PCT lack of unity guidelines. These guidelines state one means in which to show the invention lacks a special technical feature is determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim. Applicant has not provided any arguments, reasoning or evidence that Groups I-VIII are so linked into a general inventive concept. PCT rules only permit the first product, the first method of making the product and the first method of using the product to be examined together, when a special technical feature can be established.

The requirement is still deemed proper and is therefore made FINAL.

Claims 14-48 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 2/5/07.

Claims 1-13 are under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-9 are directed to a method of inhibiting inflammation in a subject in need thereof, comprising contacting cells of the subject with an active agent that induces up-regulation of RUNX3 expression in the cells. Embodiments limit the cells to thymocytes and dendritic cells (DC). Embodiments limit the active agent, to a polynucleotide encoding RUNX3 and further limitations, wherein the contact between the cells and the active agent is performed ex vivo. Claims 10-12 are directed to a method of inhibiting T cell proliferation in a subject in need thereof, comprising contacting cells of the subject with an active agent that induces up-regulation of RUNX3 expression, thereby inhibiting the T cell proliferation. Claim 13 is directed to a method of attenuating dendritic cell (DC) maturation in a subject in need thereof, comprising contacting DC of the subject with an active agent that induces up regulation of RUNX3

expression in the DC, thereby attenuating the DC maturation in said subject.

The specification discusses that the invention provides methods for treating T cell-related inflammatory conditions and testing agents for effectiveness in treating and/or preventing chronic inflammatory diseases (specification p 1, lines 5-9). The specification teaches that RUNX3 knock out mice develop a perturbed distribution of CD4+/CD8+ T lymphocytes (example 1), increased levels of IL-5 (example 2) and spontaneous eosinophilic airway inflammation (example 3). The specification also teaches increased expression of RUNX3 in an ovalbumin (OVA)-induced acute asthma mouse model developed by Topilski et al., 2002 (specification p 33-34. Figure 3.1). The specification further correlates the increased RUNX3 expression and increased pulmonary eosinophilia of the ova-treated mice to the increased pulmonary eosinophilia of RUNX3 knock out mice (specification p 33-34, example 4). The specification contemplates that up regulation of RUNX3 expression by an agent in the mature DCs in a subject in need thereof, will lead to reducing the proportion of mature DCs vs the immature DCs in said subject, thereby inhibiting inflammation (specification p, 5, lines 1-4). However, **(a)** the specification fails to correlate the OVA-induced increase in the RUNX3 expression in the bronchoalveolar lavage macrophages of mice to contacting cells in a subject with a polynucleotide encoding RUNX3 (**RUNX3 gene therapy**), in vivo, wherein increased RUNX3 expression results in inhibiting inflammation of a subject in need thereof; **(b)** the specification fails to provide any teachings with regard to contacting cells of a subject with a polynucleotide encoding RUNX3, **ex vivo**, that induces upregulation of RUNX3, in vivo, resulting in inhibiting inflammation of a subject in need thereof (**RUNX3 gene cell therapy**); **(c)** the specification fails to provide teachings with regard to contacting cells of a subject with a polynucleotide encoding RUNX3 that induces up regulation of RUNX3 expression, thereby inhibiting T cell proliferation of a subject in need thereof; **(d)** the specification fails to provide any

teachings with regard to contacting dendritic cells of a subject with a polynucleotide encoding RUNX3 that induces up regulation of RUNX3 in the dendritic cells resulting in attenuating maturation of dendritic cells in said subject. Thus, as enablement requires the specification to teach how to make and use the claimed invention, the specification fails to enable the claimed methods for inhibiting inflammation from a subject in need thereof, a chronic inflammatory disease, or a T cell-mediated autoimmune disease and tissue transplantation. It would have required undue experimentation to make and use the claimed invention without a reasonable expectation of success.

As a first issue, the claims are directed to contacting cells of a subject with a polynucleotide encoding RUNX3 that induces up regulation of RUNX3 expression resulting **in inhibition of inflammation** in a subject in need thereof. The specification teaches increased RUNX3 expression in the pulmonary macrophages of an ova-induced acute asthma mouse model (specification p 33-34, Figure 3.1). However, the specification has failed to correlate the increased RUNX3 expression in the ova-challenged mice to the contacting cells with a polynucleotide encoding RUNX3 wherein increased RUNX3 expression in vivo results in inhibiting inflammation in a subject in need thereof. The specification correlates the increased pulmonary eosinophilia in the ova-treated mice to the increased eosinophilia in the RUNX3 knock out (k/o) mice (specification p 33-34). However, the specification has not taught supplementation with a polynucleotide encoding RUNX3 would affect eosinophilia related inflammatory diseases, in vivo. **Green et al,** (Curr Opin Allergy Clin Immunol, 7: 43-50, 2007) reports that new evidence is emerging to suggest studies in patients with severe asthma have clearly demonstrated that eosinophilic infiltration is not universally present (p 44, 2nd column). The specification also teaches perturbed distribution of CD4+/CD8+ T lymphocytes, increased ratio of mature to immature dendritic cells, increased levels of IL-5 and development of asthma-

like symptoms in the RUNX3 knock out mice. However, the specification has failed to associate the RUNX3 deficiency in the RUNX3 k/o mice to susceptibility to asthma so by introducing RUNX3 in the k/o mice, wherein RUNX3 expression will result in inhibition of inflammation of said mice. Therefore, the skilled artisan would conclude that the state of art of inhibiting inflammation in a subject tin need thereof by contacting target cells in vivo with a polynucleotide encoding RUNX3 resulting in an increase in RUNX3 expression in a target cell is undeveloped and unpredictable at best. Given the lack of guidance provided by the instant specification, it would have required undue experimentation to practice the invention as claimed for inhibiting inflammation by an active agent that up regulates RUNX3 expression without a reasonable expectation of success.

As a second issue, the claims are directed to contacting cells of a subject with a polynucleotide encoding RUNX3 that induces up regulation of RUNX3 expression, in vivo, thereby **inhibiting T cell proliferation** associated with inhibiting inflammation in a subject in need thereof. The specification teaches that RUNX3 k/o mice develop perturbed distribution of CD4+/CD8+ T lymphocytes, increased ratio of mature to immature dendritic cells, increased levels of IL-5 and development of asthma-like symptoms. The specification fails to correlate the perturbed distribution of CD4+/CD8+ T lymphocytes and the increased IL-5 levels to contacting cells with a polynucleotide encoding RUNX3 in vivo, wherein increased expression of RUNX3 will mediate a T cell-mediated or IL-5 mediated inhibition of inflammation. IL-5 is involved in the Th1/Th2 pathway of inflammatory diseases up regulating antibody formation via B cells and eosinophils (**Kidd,** Alternative Medicine Review, 8(3): 223-246, 2003) (p 225, figure 1). In inflammatory diseases T cell proliferation or Th2 proliferation is associated with interferon gamma secreted by the Th1 cells, where interferon gamma inhibits proliferation of Th2 cells (**Kidd,** Alternative Medicine Review, 8(3): 223-246, 2003) (p 225, figure 1). The art also

teaches that, distinct from IL-5, novel or cytokines such as IL-9, IL-11, IL-13 and IL-25, are likely important in an inflammatory disease in regulating the Th1/Th2 pathway involved in T cell proliferation (Kidd p 234, 2nd column, 3rd paragraph). The specification has not provided evidence to correlate the perturbed distribution of CD4+/CD8+ T lymphocytes and the increased IL-5 levels in the RUNX3 k/o mice to increased expression of RUNX3 by contacting cells with a polynucleotide encoding RUNX3 resulting in inhibition of T cell proliferation in a subject in need thereof. However, the specification failed to provide guidance to correlate the increased IL-5 levels and the perturbed distribution of CD4+/CD8+ T lymphocytes in the RUNX3 k/o mice to the Th1/Th2 cytokine inflammatory biology of other species, as for example humans. The art teaches that some of the most important variables in the Th1/Th2 cytokine biology of inflammatory diseases include the species being researched, whether studies are done in vivo or ex vivo (**Kidd,** p 226, 1st column, 2nd paragraph). **Walsh** (Current Pharmaceutical Design, 11: 3027-3038, 2005) reports that disappointing results with humanized anti-IL-5 mAbs casts doubts on the role of the eosinpophil in asthma (p 3030, 1st column, last paragraph) and eosinophils are important in pro-inflammatory cells in asthma pathogenesis rather than inflammatory cells. Thus, the specification has not taught how increased levels of IL-5 in the Runx3 k/o mice relate to T cell proliferation and increased eosinophilia and whether the introduction of RUNX3 in the k/o mice will result in the inhibition of inflammation by regulating eosinophilia thru the Th1/Th2 pathway. At the time of the instant invention asthma is largely a Th2-driven disease, but much of this story is incomplete (Kidd, p 234, 2nd column, last paragraph).

As a third issue, with regard to contacting dendritic cells of a subject with a polynucleotide encoding RUNX3 that induces up regulation of RUNX3 in the dendritic cells resulting in **attenuating maturation of dendritic cells** of said subject, the art teaches the role of dendritic cells in pulmonary inflammation is unpredictable. The specification teaches

increased ratio of mature to immature dendritic cells, in the RUNX3 k/o mice associated with asthma-like symptoms and inflammatory diseases. The specification contemplates that when Runx3 is lost, epidermal Langerhans cells (LC) are absent and RUNX3 k/o DCs display accelerated maturation due to lack of responsiveness to TGF-beta and over-responsiveness to maturation inducing stimuli (specification, p 18). However, the specification fails to provide guidance to correlate the increased ratio of mature dendritic to immature dendritic cells in the k/o mice to contacting dendritic cells with a polynucleotide encoding RUNX3 in vivo resulting in attenuating maturation of dendritic cells and inhibition of inflammation, in a subject in need thereof. For example, in pulmonary inflammatory diseases, the art teaches that a more detailed phenotypic analysis of dendritic cells in their role of inflammatory processes in the pathogenesis of pulmonary arterial hypertension (PAH) will have to be performed (**Lambrecht et al,** Eur Respir J, 29: 435-437, 2007) p 436, 2nd column, last paragraph). The lack of significant effects of systemic steroids in idiopathic PAH patients provides an argument against the role of DCs in PAH (**Lambrecht,** p 436, 2nd column, last paragraph). **Lambrecht et al,** reports that the most important question even in 2007 is what is the functional role of dendritic cells in PAH (p 436, 1st column, 2nd paragraph). **Wallet et al,** (Clinical Medicine & Research, 3(3): 166-178, 2005) reports that the molecular targets of TGF-beta mediated suppression in DCs remain ill defined and one such target appears to be the RUNX3 transcription factor (p 170, 1st column, 2nd paragraph). **Wallet et al,** (Clinical Medicine & Research, 3(3): 166-175, 2005) indicates that primarily a contrasting role of DCs has been described as a function of maturation where immature DCs were largely considered to be non-inflammatory or tolerogenic, but mature dendritic cells were considered capable of eliciting a pro-inflammatory immune responses and although generally correct, this paradigm is now proving too simple (p 166, 1st column). This

issue is further complicated by the identification of distinct subtypes of dendritic cells that exhibit different antigen-presenting cell effector functions (abstract).

With regard to contacting cells in a subject with a polynucleotide encoding RUNX3 (RUNX3 gene therapy), in vivo, wherein increased RUNX3 expression will result in inhibiting inflammation in a subject in need thereof as contemplated by the specification the state of the art for inhibiting inflammation by gene therapy is unpredictable. In general, with regard to the gene therapy, while progress has been made in recent years for gene transfer in vivo, vector targeting to desired tissues in vivo continuous to be a limitation as supported by numerous teachings in the art. Numerous factors complicate the gene delivery art, which would not have been shown to overcome by routine experimentation. These include, the fate of the DNA vector itself (volume of distribution, rate of clearance into tissues, etc), the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRMA produced, the stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically on the vector being used and the protein being produced. While progress has been made in recent years for in vivo, gene transfer, vector targeting in vivo to desired organs continuous to be unpredictable and inefficient. **Zhou et al,** (Medicinal Research Reviews, 24(6): 748-761, 2004) even after the filing of the instant application indicates that gene therapy requires gene systems with less toxicity and immunity, high efficiency in gene transfer and the therapeutic gene expression in the targeted cells or tissues at functional level in a controllable manner (p 748, last paragraph). Zhou also notes to date, however, the gene delivery systems, including non-viral and viral vectors have somewhat immunogen inducing the host immune responses in gene therapy, which is one of the challenges of gene therapy (p 749,

1st paragraph). Zhou teaches that despite considerable progress over the past decade in the generation of gene transfer systems with reduced immunogenic properties, the remaining immunogen of many gene therapy vectors is still the major hurdle preventing their application in clinical trials, because the host immune responses induced by immunogen of the vectors lead to low level and short term of transgene expression, inefficient re-administration of the same vectors and severe side-effects in clinical trials (p 752, last paragraph). Zhou teaches that mice injected either intraperitoneal, intravenous or subcutaneously with rAAV-OVA developed strong OVA-specific CTL response, however, mice injected intramuscularly with the same virus developed minimal CTL response (p 755, 2nd paragraph). The specification however, has not provided any specific guidance or teachings with regard to the other modes of cell targeting or modes of administering RUNX3 therapeutic gene encompassed by the claims. With regard to the contact between the cells and the polynucleotide encoding RUNX3 is performed ex vivo, the art teaches that the purity of DC produced in vitro is questionable, and cultures could contain DC in different stages of development or other unknown contaminant cell types (**O'Neil et al,** Journal of Leukocyte Biology, 75: 600-603, 2004) (p 602, 2nd column, last paragraph). DC produced from different starting cell populations, such as monocytes and BM or cord blood can vary in their functional capacity (p 602, 2nd column, last paragraph).

In light of the above, the state of the art is suggesting that contacting cells of a subject with a polynucleotide encoding RUNX3 in vivo that induces up regulation of RUNX3 expression in the cells resulting in inhibiting inflammation might be feasible in the future. The instant specification does not provide any relevant teachings, specific guidance, or working examples for overcoming the limitations of RUNX3 gene therapy or ex vivo dendritic cell RUNX3 gene therapy raised by the state of the art. Therefore, the skilled artisan would conclude that the state of art of RUNX3 gene therapy is undeveloped and unpredictable at best. Given the lack of

guidance provided by the instant specification, it would have required undue experimentation to practice the invention as claimed for inhibiting inflammation by RUNX gene therapy without a reasonable expectation of success.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for inhibiting inflammation by RUNX3 gene therapy, RUNX3 gene therapy ex vivo, or dendritic cell RUNX3 gene therapy, the lack of direction or guidance provided by the specification for inhibiting inflammation by RUNX3 gene therapy, RUNX3 gene therapy ex vivo, or dendritic cell RUNX3 gene therapy, the unpredictable state of the art with respect to RUNX3 gene therapy, RUNX3 gene therapy ex vivo, or dendritic cell RUNX3 gene therapy, the undeveloped state of the art pertaining to the inhibition of inflammation by RUNX3 gene therapy, RUNX3 gene therapy ex vivo, or dendritic cell RUNX3 gene therapy, and the breadth of the claims directed to all inflammatory diseases, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

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